

HED DOC. NO. 014312

**DATE:** 8/28/00

**MEMORANDUM**

**SUBJECT:** *Hydroxyatrazine* - Report of the Hazard Identification Assessment Review Committee.

**FROM:** Roger Hawks, Toxicologist.  
Reregistration Branch III  
Health Effects Division (7509C)

**THROUGH:** Jess Rowland, Co-Chair  
and  
Elizabeth Doyle, Co-Chair  
Hazard Identification Assessment Review Committee  
Health Effects Division (7509C)

**TO:** Cathy Eiden, Risk Assessor  
Reregistration Branch III  
Health Effects Division (7509C)

**PC Code:** None (the compound is a common metabolite of the triazine herbicides atrazine, simazine and propazine). File under atrazine, PC Code 080803.

On May 4, 2000, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for hydroxyatrazine with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to hydroxyatrazine was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996. The conclusions drawn at this meeting are presented in this report.

## Committee Members in Attendance

Members present were:

Elizabeth Mendez, David Nixon, Yung Yang, Beth Doyle, Jonathon Chen, Jess Rowland, Brenda Tarplee, Bill Burnam, Vicki Dellarco, Pam Hurley

Member(s) in absentia: Tina Levine

Data evaluation prepared by: Roger Hawks, Reregistration Branch III

Also in attendance were: Karl Baetcke, HED Richard Hill, OPPTS

Data Evaluation / Report Presentation

---

Roger Hawks  
Toxicologist

## 1. **INTRODUCTION**

On May 4, 2000, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for hydroxyatrazine with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to hydroxyatrazine was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996. The conclusions drawn at this meeting are presented in this report.

## 2. **HAZARD IDENTIFICATION**

### 2.1 **Acute Reference Dose (RfD)**

HIARC did not select an endpoint for any population for the acute RfD. The only effects seen in any of the submitted studies which may be attributable to a single dose were the development alterations in the developmental rat study. The developmental alterations seen in this study were seen only at the high dose, were few in number, and were not deemed by HIARC to be of toxicological significance. No other study in the database was found to have effects which could be attributed to a single exposure.

Thus, HIARC concludes that no toxicologically significant endpoint to represent a single exposure can be found in the toxicology database for hydroxyatrazine.

### 2.2 **Chronic Reference Dose (RfD)**

Study Selected: Combined chronic/carcinogenicity in rats

Guideline #: 83-5

MRID No.: 43532001

Executive Summary:

In a 2-year combined chronic feeding/carcinogenicity study, G-34048 technical (hydroxyatrazine) of 97.1% purity was administered in the diet to groups of 70 or 80 male and 70 or 80 female Crl:CD (SD) BR strain rats at dose levels of 0 (control), 10, 25, 200 or 400 ppm (equivalent to 0, 0.388, 0.962, 7.75, or 17.4 mg/kg/day in males and to 0, 0.475, 1.17, 9.35, or 22.3 mg/kg/day in females). Ten or 20 rats/sex/group were sacrificed at 12 months; the remaining 60 animals in each group were scheduled to be sacrificed at 24 months. Due to high mortality in the 400 ppm group, however, the surviving males and females in the 400 ppm group were sacrificed at 18 months. Mortality, clinical signs of toxicity, body weights, food consumption and water consumption were monitored. Ophthalmologic examinations were performed. Hematological examinations, clinical chemistries and urinalysis were also performed. Necropsy examinations were conducted on all animals

and organ weight determinations were made on all animals sacrificed at 12, 18, 24 months. Histopathological examinations were made on a complete set of organs/tissues from all animals in the control, 200 and 400 ppm groups. Histopathological examinations were also performed on a limited set of organs/tissues from the 10 and 25 ppm groups.

At 400 ppm, an excessive treatment-related mortality was observed for both males and females and this dose level was terminated at 18 months. Severe renal failure was the predominant cause of death for these animals. Prior to death or sacrifice, these animals exhibited emaciation, dehydrated bodies, pallor and other clinical signs of toxicity expected in animals with severe renal failure. Greatly decreased body weights, body weight gains and food consumption were observed in these animals throughout the study (to 18 months). Water consumption was increased during the first year of the study. Changes in hematology parameters (including anemia), in clinical chemistries parameters (indicating renal disturbances) and in urinalysis parameters (including crystalline material in urine samples) were observed in 400 ppm males and females. Gross necropsies, organ weights and histopathology indicated that kidney and lower urinary tract were the primary target organs in both males and females at 400 ppm. Kidney effects included discoloration, calculi and rough pitted surfaces seen at gross necropsy; increased kidney weights; and severe histopathological changes including deposition of crystalline material within collecting ducts and renal pelvises, calculi, other morphological changes and accelerated chronic progressive nephropathy. In addition, secondary effects in extra renal tissues reflected the severe renal damage and resulting renal failure in these animals.

At 200 ppm, similar but less severe gross and histopathological effects on the kidneys were observed in both males and females. Secondary effects in extra renal tissues were generally not observed at this dose level.

At 25 ppm, no treatment-related effects were observed in either male or female rats. An accumulation of interstitial matrix in the papilla of the kidneys of female rats was observed at this dose level, but the toxicologic significance of this observation, in the absence of any other signs of renal damage or impaired renal function, was highly questionable.

A treatment-related increased incidence of tumors of any type was not observed in the treated male or female animals in this study. In particular, there was no increase above control levels in the incidence of mammary gland tumors in either males or females. In addition, onset times for mammary gland tumors in female rats were not decreased in this study.

**For both male and female rats, the NOAEL is 25 ppm (0.962 mg/kg/day for males and 1.17 mg/kg/day for females) and the LOAEL is 200 ppm (7.75 mg/kg/day for males and 9.53 mg/kg/day for females), based on gross and histopathological effects in the kidneys.**

This study is classified as **Acceptable-Guideline** and does satisfy the 83-5 guideline requirement for a combined chronic/carcinogenicity toxicity study.

Dose and Endpoint for Establishing RfD: 1.0 mg/kg/day based on kidney alterations seen at the LOAEL of 7.75 mg/kg/day in males and 9.53 mg/kg/day in females.

Uncertainty Factor(s): 100

Comments about Study/Endpoint/Uncertainty Factor: This dose chosen is the NOAEL in males rounded up to 1.0.

$\text{Chronic RfD} = \frac{1.0 \text{ mg/kg/day}}{100} = 0.01 \text{ mg/kg/day}$
---

## 2.3 Occupational/Residential Exposure

### 2.3.1 Short-Term (1-7 days) Incidental Oral Exposure

Study Selected: Developmental toxicity study in the rat §83-3

MRID No.: 41065202

Executive Summary (this executive summary reflects the HIARC decision):

In a developmental toxicity study (MRID 41065202) hydroxyatrazine, 97.6% a.i., was administered to 104 Sprague-Dawley females, 26/dose, by gavage at dose levels of 0, 5, 25, or 125 mg/kg/day from days 6 through 15 of gestation.

There were no maternal deaths in this study. Two of the 22 pregnant females in the high dose group had enlarged, mottled kidneys, findings which were not seen in any other animal and are considered compound-related. Food consumption was significantly decreased (8.7%;  $p < 0.05$ ), at the high dose group only, during the 6-16 day dosing period. Body weight and body weight gain were unaltered by atrazine treatment. There were no clinical signs attributable to compound exposure. There were no alterations in cesarean section parameters in dose groups *vs* controls.

**The maternal LOAEL is 125 mg/kg/day, based on decreased food consumption during the dosing period and enlarged and mottled kidneys. The maternal NOAEL is 25 mg/kg/day.**

Fetal death and resorptions were not altered by compound exposure. The high dose group only displayed increases in partially ossified interparietals (control fetal/litter incidence of 20%/56% *vs* high dose fetal/litter of 44%/91%); partially ossified hyoid (control fetal/litter 6%/20%, *vs* 17%/55%). Mean male and female fetal body weight at the high dose was significantly ( $p < 0.05$ ) reduced compared to controls (Control male/female body weight 3.6/3.4 grams *vs* male/female high dose 3.5/3.3 grams. There were no increases in any visceral findings in dosed fetuses.

The increases in partially ossified interparietals and hyoid bones are not considered to be of toxicologic significance. Fetal body weights are only decreased one-tenth of a gram, and are also not considered to be toxicologically significant.

**The developmental LOAEL is 125 mg/kg/day, based on increased incidence of partially ossified interparietal and hyoid bones and decreased fetal body weight. The developmental NOAEL is 25 mg/kg/day.**

The developmental toxicity study in the rat is classified **Acceptable-Guideline** and does satisfy the guideline requirement for a developmental toxicity study (OPPTS 870.3700; §83-3a) in the rat.

Dose and Endpoint for Risk Assessment: 25 mg/kg/day based upon decreased food consumption and kidney alterations seen at the next highest dose of 125 mg/kg/day.

Comments about Study/Endpoint: This endpoint is viewed as indicative of general or systemic toxicity and is thus appropriate for the population (infants and children) of concern.

### **2.3.2 Intermediate-Term (7 Days to Several Months) Incidental Oral Exposure**

Study Selected: Subchronic oral toxicity (rat) Guideline #: 82-1

MRID No.: 41293501

#### Executive Summary:

In a subchronic toxicity study (MRID 41293501) hydroxyatrazine (97.1% ) was administered to 150 Sprague-Dawley rats, 15/sex/dose in the diet at dose levels of 0, 10, 100, 300 and 600 ppm (0, 0.64, 6.3, 18.89 and 37.47 mg/k/g/day for males and 0, 0.75, 7.35, 22.75 and 45.64 mg/kg/day for females).

With the exception of kidney alterations, most of the adverse effects of hydroxyatrazine exposure were limited to the high dose group. Body weights were non-significantly reduced in both sexes at the high dose only (7% reduction compared to controls in males and 5% reduction in females). Percent body weight gain was significantly decreased in both sexes at the high dose only (14.4% decrease compared to controls in males and 13.6% in females). Food consumption was significantly decreased in males only and only at a few selected timepoints. Hematocrit and erythrocyte counts were significantly depressed in both sexes at the high dose only (-7.2% and 7.6% in males and females respectively for hematocrit and -5.4% and 4.4% for males and females respectively for red blood cell counts). Hemoglobin was also significantly decreased in high dose males only (-6.4% compared to controls). Serum blood urea nitrogen was significantly increased in both sexes at the high dose only (+76% in males, +79.6% in females) as was creatinine (+38% in both sexes) sodium (+1.4% in males, +0.7% in females) and chloride (+2% in males, + 2.9% in females). Urine volume was significantly increased in both sexes at the high dose (+227% in males and +147% in females compared to controls). Urine volume was also significantly increased in males in the 300 ppm group (+38% compared to controls). Kidney weights - absolutely and relative to both body and brain weight - were significantly increased in both sexes at the high dose only. Kidney weights relative to body weight were increased 44% in males and 45% in females compared to controls.

Kidney alterations at both gross necropsy and at histopathology were seen in both the 300 and 600 ppm dose groups. Toxic nephrosis classified as "minimal" was seen in 7 of 15 males and 11 of 15 females at 300 ppm. Toxic nephrosis classified as severe was seen in all animals of both sexes at the high dose. Tubule crystals were seen in 10 of 15 males and 11 of 15 females at the high dose.

There were no compound-related effects in mortality, clinical signs, or ophthalmology in either sex at any dose.

**The LOAEL is 300 ppm (18.9 mg/kg/day in males and 22.75 mg/kg/day in females) , based on kidney alterations . The NOAEL is 100 ppm (6.3 mg/kg/day in males and 7.35 mg/kg/day in females).**

This subchronic toxicity study is classified **Acceptable-Guideline** and does satisfy the guideline requirement for a subchronic oral study (82-1) in the rat.

Dose and Endpoint for Risk Assessment: 6.3 mg/kg/day based on kidney alterations seen at the next highest dose.

Comments about Study/Endpoint: The subchronic dog study provides support for the selection of this endpoint. The NOAEL in the subchronic dog study (MRID 41547901) was 5.8 in males and 6.2 females based on body weight decreases and kidney alterations seen at the next highest dose. Thus, the dose and effects seen in the 90 day dog are similar to the dose and effects seen in the 90 day rat.

### **2.3.3 Dermal Absorption**

*Based on SAR, the studies and dermal absorption factor selected are identical to those selected for atrazine*

Dermal Absorption Factor: **The committee recommended a dermal absorption factor of 6% (rounded up from 5.6%).** This factor is based on a human study (MRID 44152114) in which 10 human volunteers were exposed to a single topical dose of [triazine ring-U-<sup>14</sup>C]atrazine (94.3-96.3% a.i., 98.0-98.4% radiochemical purity) at 6.7 (4 volunteers) or 79 : g/cm<sup>2</sup> (6 volunteers) for 24 hours; equivalent to 0.1667 and 1.9751 mg of [14C] atrazine for the low and high doses, respectively. After 24 hours the atrazine was removed and determination of percent absorbed occurred was determined 168 hours (7 days) after the commencement of exposure. The maximum percent absorbed in this study was 5.6% of the dose in the lower dose group. Because the maximum percent absorbed is being used and because an ample amount of time (168 hours) was allowed for absorption to occur, 6% is deemed to be a protective estimate of dermal exposure.

Dermal Absorption Factor: 6%

### **2.3.4 Short-Term Dermal (1-7 days) Exposure**

### **Short-Term Dermal (1-7 days) Exposure**

Study Selected: Developmental Toxicity (Rat) Guideline #: 83-3

MRID No.: 41065202

Executive Summary: See above under "Short-Term (1-7 days) Incidental Oral Exposure"

Dose and Endpoint for Risk Assessment: 25 mg/kg/day based on decreased maternal food consumption and kidney alterations at the next highest dose of 125 mg/kg/day.

Comments about Study/Endpoint: No dermal toxicity studies are available. The dosing regimen in this study is appropriate for the exposure period of concern. Since an oral NOAEL was selected, the 6% dermal absorption factor should be used for route-to- route extrapolations.

### **2.3.5 Intermediate-Term Dermal (7 Days to Several Months) Exposure**

Study Selected: Subchronic oral toxicity (rat) Guideline #: 82-1

MRID No.: 41293501

Executive Summary: See above under: "Intermediate-Term (7 days to Several Months) Incidental Oral Exposure".

Proposed Dose and Endpoint: 6.3 mg/g/day based on kidney alterations seen at the next highest dose.

Comments about Study/Endpoint: The subchronic dog study provides support for the selection of this endpoint. The NOAEL in the subchronic dog study (MRID 41547901) was 5.8 in males and 6.2 females based on body weight decreases and kidney alterations seen at the next highest dose. Thus, the dose and effects seen in the 90 day dog are similar to the dose and effects seen in the 90 day rat. Since an oral NOAEL was selected, the 6% dermal absorption factor should be used for route-to- route extrapolations.

### **2.3.6 Long-Term Dermal (Several Months to Life-Time) Exposure**

Study Selected: Combined chronic/carcinogenicity in rats

Guideline #: 83-5

MRID No.: 43532001

Executive Summary: See above under "CHRONIC DIETARY [Reference Dose (RfD)]"

Dose and Endpoint Proposed for Consideration: 0.962 mg/kg/day (*rounded to 1.0*) based on renal

toxicity seen at the next highest dose.

Comments about Study/Endpoint: No dermal or inhalation toxicity studies are available. This is the same study/endpoint used for establishing the RfD. Since an oral NOAEL was selected, the 6% dermal absorption factor should be used for route-to-route extrapolations.

### **2.3.7 Inhalation Exposure (All Durations)**

No inhalation studies are available for evaluation. Therefore the HIARC selected the oral NOAELs for inhalation risk assessments. Since an oral dose is used, risk assessment should follow the route-to-route extrapolation as below:

- Step I. The inhalation exposure component (i.e : g a.i./day) using 100% absorption rate (default value) and application rate should be converted to an equivalent oral dose (mg/kg/day).
- Step II. The dermal exposure component (mg/kg/day) using a 6% dermal absorption rate and application rate should be converted to an equivalent oral dose. This dose should then be combined with the oral equivalent dose in Step I.
- Step III. The combined oral equivalent dose from Step II should then be compared to the oral NOAELs to calculate MOEs. The NOAELs are as follows:

For short term: 25 mg/kg/day  
For intermediate term: 6.3 mg/kg/day  
For chronic exposures: 1.0 mg/kg/day

### **2.3.8 Margins of Exposure for Occupational/Residential Risk Assessments**

The level of concern for occupational exposure risk is an MOE of 100.

The levels of concern (*i.e.*, MOEs) for residential exposure risk will be determined by the FQPA SF committee.

## **3 CLASSIFICATION OF CARCINOGENIC POTENTIAL**

- 3.1 **Combined Chronic Toxicity/Carcinogenicity Study in Rats:** This study not available.
- 3.2 **Carcinogenicity Study in Mice:** This study not available.

- 3.3 Classification of Carcinogenic Potential:** Hydroxyatrazine has not been classified as to its carcinogenic potential by the HED Cancer Peer Review committee. The HED Metabolism Committee concluded in a September 29, 1995 meeting that: "For Atrazine, the residues of concern for cancer dietary risk are parent and chloro metabolites". Hydroxyatrazine is not a chlorometabolite and is not considered by the HED metabolism committee to possess carcinogenic potential

## **4 MUTAGENICITY**

The test material did not induce any increases in revertant colonies of four Salmonella strains exposed to precipitating concentrations 313 : g/plate and above), activation system was present or not. This study is classified **Acceptable-guideline**.

Hydroxyatrazine, a metabolite of atrazine, did not cause an increase in micronuclei in mice treated with acute intubated doses up to 500 mg/kg (limit test). No mortality, clinical signs of toxicity as measured by MCE/PCE ratio was observed at any sample time (up to 48 hr.). This study satisfied the guidelines for micronucleous testing and was performed in a satisfactory manner for regulatory purposes, but since there was no observed cytotoxicity, it did not provide definitive evidence that hydroxyatrazine is not a mutagen. This study is classified **Acceptable-guideline**.

No evidence of unscheduled DNA synthesis was found in primary hepatocyte cultures treated *in vitro* (in two separate experiments) with hydroxyatrazine at concentrations approaching toxicity (1500 : g/mL) and/or associated with preparation of test substance. This study is classified **Acceptable-guideline**.

Reportedly negative in human fibroblast cells treated with hydroxyatrazine up to the limits of solubility (increasing precipitation from 500 : g/mL) and severe cytotoxicity (1500 : g/mL). The study is acceptable and the negative results considered valid, but only in the absence of metabolic activation. The substance was not tested with activation. This study is classified **Acceptable-Non-guideline**.

The available evidence indicates that hydroxyatrazine is non-mutagenic.

## **5 FQPA CONSIDERATIONS**

- 5.1 Adequacy of the Data Base** The toxicology database for hydroxyatrazine was considered adequate by the HIARC for consideration of factors under FQPA. Because of the structural similarities between atrazine and hydroxyatrazine, it is assumed that hydroxyatrazine will not display any qualitative differences in factors of concern in regards to FQPA (the only evident qualitative difference in toxicity between hydroxyatrazine and atrazine is that hydroxyatrazine has a propensity to crystallize resulting in kidney toxicity). Thus, information from the atrazine

toxicology database may be used to gain a better understanding of potential hydroxyatrazine toxicities.

- 5.2 Neurotoxicity** There is no evidence of neurotoxicity from the submitted toxicity studies. Numerous studies from the registrant and the open literature have demonstrated neuroendocrine toxicity for the parent atrazine compound. The neuroendocrine effects described for atrazine are postulated to be part of a cancer mode of action for atrazine (this hypothesis is to be presented to the Agency's SAP for consideration in June of 2000). Because hydroxyatrazine is non-carcinogenic, the current belief is that the neuroendocrine effects described for atrazine are not occurring following hydroxyatrazine exposure.
- 5.3 Developmental Toxicity** There is no evidence for increased susceptibility of rat fetuses to *in utero* exposure in a rat developmental study. A developmental study in the rabbit is not available.
- 5.4 Reproductive Toxicity** A multi-generation reproduction study is not available.
- 5.5 Additional Information from Literature Sources** None are available
- 5.6 Determination of Susceptibility** There are no rabbit developmental toxicity studies and there is no multi-generation reproduction study. The data from the rat prenatal developmental toxicity study showed a statistically significant decrease in fetal weights and increase in incompletely ossified interparietals and hyoid bones. HIARC determined that these findings lacked toxicologic significance. An increased sensitivity of the fetus to hydroxyatrazine exposure *in utero* was not seen in the available study.
- 5.7 Recommendation for a Developmental Neurotoxicity Study**

**5.7.1** Evidence that suggest requiring a Developmental Neurotoxicity study:

Special studies and an open literature study mentioned above indicate a neuroendocrine toxicity in the CNS of rats following atrazine exposure.

**5.7.2** Evidence that **do not** support a need for a Developmental Neurotoxicity study:

Overt signs of neurotoxicity were not seen in the submitted toxicology studies. The neuroendocrine alterations mentioned above would not be expected to be seen following hydroxyatrazine exposure. These alteration have been proposed to be central to the mode of action for atrazine associated rodent carcinogenesis and hydroxyatrazine is not carcinogenic (the proposed mode of action for atrazine associated carcinogenesis, including these neuroendocrine alterations, is being presented to the SAP for consideration in June of 2000). Thus, one can reasonably assume that these neuroendocrine alterations

will not occur following hydroxyatrazine exposure.

## **6      HAZARD CHARACTERIZATION**

Hydroxyatrazine is a metabolite of atrazine, simazine and propazine. Both plants and mammals are capable of metabolizing these compounds to hydroxyatrazine, though in mammals hydroxyatrazine is a minor metabolite while in plants it is the major metabolite. Bacteria are also able to metabolize atrazine, simazine, and propazine to hydroxyatrazine.

The available guideline subchronic, chronic/onco, and developmental studies indicated that the kidney is the primary target organ for hydroxyatrazine associated toxicity. Hydroxyatrazine appears to crystallize in the serum leading to the formation in the blood stream of hydroatrazine crystals. These crystals cause direct physical damage to the kidney. This crystallization phenomenon has not been observed with atrazine or any of the chlorometabolite of atrazine. Several studies have indicated that atrazine is associated with mammary and pituitary tumors in females of the Sprague-Dawley strain of rat. The HED metabolism committee has stated that atrazine and the chlorometabolites of atrazine are of carcinogenic concern. Hydroxyatrazine is not a chlorometabolite of atrazine and is not expected to be of carcinogenic concern.

The mutagenicity database for hydroxatrazine is adequate and indicates that hydroxyatrazine atrazine is not mutagenic.

## **7      DATA GAPS**

Hydroxyatrazine is metabolite of registered pesticides and is not a registered pesticide itself. Registration is not being sought for hydroxyatrazine. Thus, a full toxicology database consisting of guideline FIFRA Series 81 - 85 or OPPTS 870 Series studies are not required for hydroxyatrazine. Some guideline studies using hydroxyatrazine have been submitted to the agency. These studies, in conjunction with the toxicology studies from atrazine - the structurally similar parent of - have been used by HIARC to evaluate the potential toxicity of hydroxyatrazine exposure. HIARC has reviewed the toxicology available studies for hydroxyatrazine, in conjunction with the atrazine toxicology database, and has found that there are currently no data gaps for hydroxyatrazine.

## **8      ACUTE TOXICITY**

Acute toxicity studies with hydroxyatrazine are not available for evaluation

## 9 SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	NOAEL= None selected	None selected	None selected
	Acute RfD = Not determined		
Chronic Dietary	NOAEL = 1.0 UF = 100	Renal alterations	Combined chronic toxicity/oncogenicity in the rat
		Chronic RfD = 0.01	
Incidental Oral, Short-Term	NOAEL= 25	Decreased food consumption and renal effects in the dams	Developmental toxicity in the rat
Incidental Oral, Intermediate-Term	NOAEL= 6.3	Renal alterations	90-day study in the rat
Dermal, Short-Term <sup>a</sup>	NOAEL= 25	Decreased food consumption and renal effects in the dams	Developmental toxicity in the rat
Dermal, Intermediate-Term <sup>a</sup>	NOAEL= 6.3	Renal alterations	90-day study in the rat
Dermal, Long-Term <sup>a</sup>	NOAEL= 1.0	Renal alterations	Combined chronic toxicity/oncogenicity in the rat
Inhalation, Short-Term <sup>a</sup>	NOAEL= 25	Decreased food consumption and renal effects in the dams	Developmental toxicity in the rat
Inhalation, Intermediate-Term <sup>b</sup>	NOAEL= 6.3	Renal alterations	90-day study in the rat
Inhalation, Long-Term <sup>b</sup>	NOAEL= 1.0	Renal alterations	Combined chronic toxicity/oncogenicity

a Dermal absorption rate = 6%

b Convert from oral dose using an inhalation absorption rate= 100% default